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| 10/524,278 | 03/15/2005 | Hiroshi Sato | 3190-074 | 4130 |

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| EXAMINER | |
|---|---|
| GOLDBERG, JEANINE ANNE | |
| **ART UNIT** | **PAPER NUMBER** |
| 1634 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/524,278 | SATO ET AL. | |
| | Examiner | Art Unit | |
| | Jeanine A. Goldberg | 1634 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1,2,5-16 and 18-22* is/are pending in the application.

4a) Of the above claim(s) *7-9,11,12,14-16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,6,10,13 and 19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. This action is in response to the papers filed October 23, 2007. Currently, claims 1-2, 5-16, 18-22 are pending. Claims 7-9, 11-12, 14-16, 18 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. **This action is FINAL.**

### *Election/Restrictions*

4. Applicant's election without traverse of Group I, Claims 1-6, 10, 13, 17, 19 in the paper filed November 30, 2006 is acknowledged.

The response asserts that the corresponding International application has found unity of invention and that the unity of invention should apply in the instant application. This argument has been reviewed but is not persuasive because the two groups lack a special technical feature. The prior art, namely Huang (Pharmacokinetics, Vol. 10, pages 539-544, 2000) specifically teaches the polymorphism in the UGT gene, exon 5, nucleotides 1456 and amino acid position 486. Thus, this polymorphism is not a contribution over the prior art.

Unity of invention considerations do not require burden on the part of the examiner. However, even if burden was required to be established in an international stage application, search of the nucleic acids and search of the methods are not

coextensive. A search of the nucleic acid does not require a search of drug metabolizing activity required by group I.

Claims 7-9, 11-12, 14-16, 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims 7-9, 11-12, 14-16, 18 are drawn to an invention nonelected with traverse in the paper filed November 30, 2006. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

### *Priority*

5. This application is a 371 of PCT/JP03/01475, filed February 13, 2003 and foreign priority application 2002-235029, filed August 12, 2002.

### *Drawings*

6. The drawings are acceptable.

### *Claim Rejections - 35 USC § 112- Enablement*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 5-6, 10, 13, 19-22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

The claims are drawn to an assay method for drug metabolizing activity of UGT comprising a step of detecting a mutation in exon 5 region of a gene coding for UGT.

The claims broadly encompass any mutation, any drug metabolizing activity in any organism.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches genetic variations and associations are often irreproducible.

Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that

the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification teaches uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases, UGT) are enzymes that catalyze glucuronidation of various drugs (page 1). The specification teaches that the different UGT enzymes conjugate different substrates (page 1-2). The specification analyzes 2-amino-5-nitro-4-trifluoromethylphenol glucuronide which is glucuronidated by UGT. The specification states that "as long as drugs to be assayed by the invention are glucuronidated by UGT, they are useful for assay of their metabolism" (page 15, lines 20-26). The specification provides a short list of examples (page 15-16). The specification measured UGT activity with bilirubin and 2-amino-5-nitro-4-trifluoromethylphenol glucuronide as a substrate (page 20). The UGT1A1 molecule UGT gene mutation Y485D (homozygous) was 8% UGT relative activity (page 20). The UGT1A1 molecule UGT gene mutation Y485D (heterozygous) was 36%. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention as broadly as claimed.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied

The claims are drawn to any glucuronidation of UGT. The specification teaches that uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases, UGT) are enzymes that catalyze glucuronidation of various drugs (page 1). The specification teaches that the different UGT enzymes conjugate different substrates (page 1-2). The specification analyzes a single drug, namely 2-amino-5-nitro-4-trifluoromethylphenol glucuronide which is glucuronidated by UGT. However this single drug is not representative of the class of drugs glucuronidated by UGT. The skilled artisan would be required to perform additional experimentation on the other members of the class of drugs that are affected by UGT to determine whether the polymorphisms in UGT, including the exon 5 mutation at 1456 of the instant specification, are associated with drug glucuronidation of UGT.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art of associating polymorphisms with particular condition, the broad scope of the claims would not be enabled at the time the invention was made. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized.
Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these

unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

**Response to Arguments**

The response traverses the rejection. The response asserts that since a drug undergoes glucuronidation by UGT in order to be metabolized, drug metabolism can also be predicted by detecting such mutations. The response further asserts that the enzymatic reactions in glucuronidation of a particular drug by normal molecules of the isoforms UGT1A1 and UGT1A6 were compared with molecules having the Y486 mutation. Finally the response provides Kurkela to support the position that mutations in Y483D of UGT1A9 and Y486D of UGT1A1 affect other drugs.

This argument has been thoroughly reviewed and deemed not persuasive. First, the specification does not appear to analyze both UGT1A1 and UGT1A6 isoform with respect to the same substrate. Table 1, page 20, appears to be directed to UGT1A1 molecules with the bilirubin substrate. Moreover, Table 2, page 21, appears to be UGT1A6 molecules with 2-amino-5-nitro-4-trifluoromethylphenol as a substrate. The specification does not appear to analyze UGT1A3, UGT1A4, UGT1A5, UGT1A7, UGT1A8 or UGT1A9. Thus, it is unpredictable whether these isoforms would have similarly enzyme activity in response to drug glucuronidation.

Second, Kurkela, as provided by the response, does not appear to support applicants assertion that mutations in Y483D of UGT1A9 which corresponds to Y486D of UGT1A1 are predictably associated with the class of drugs encompassed by the claims. Kurkela specifically teaches Y486D mutation was shown to reduced the activities of the UGT1A1 and UGT1A6. However, Surprisingly, the corresponding mutation in the UGT1A9 doubled the Vmax of scopoletin glucuronidation, where as entacapone glucuronidation rate was decreased (abstract). Thus, there is no predictable nature of the glucuronidation between isoforms or different drugs. Kurkela suggests that the Y to D mutation in UGT1A9 might not be detrimental to enzymatic activity, thereby revealing isoform-specific differences due to extensive protein-protein interactions (page 2444, col. 1). Kurkela analyzes the activities of 1A9/Y483D towards scopoletin and entacapone (see Figure 2). The activity and kinetics results clearly show that in sharp contracts to the previous results with UGTs 1A1 and 1A6, the Y483 mutation increased the activity of UGT1A9, at least as far as scopoletin glucuronidation is concerned (page 2446, col. 1). Simply, the mutation affected the scopoletin and entacapone glucuronidation activities of UGT1A9 in different and opposite ways (page 2446, col. 2). Thus, it is clear that there is no predictability between isoforms and different drugs. The specification provides a single example of a single drug that glucuronidates, however, this single drug does not provide enablement and predictability for the class of drugs that cause glucuronidation of UGT. Thus for the reasons above and those already of record, the rejection is maintained.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1-2, 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Huang et al. (Pharmacogenetics, Vol. 10, pages 539-544, 2000).

Huang et al teaches variations of the bilirubin uridine-diphosphoglucuronosyl transferase 1A1 gene in healthy Taiwanese individuals. Huang teaches activity of UGT1 may influence the concentration of serum bilirubin. Huang teaches a variation site in UGT1A1 gene in exon 5, at nucleotides 1456 which is a TAC to GAC substitution which corresponds to the amino acid substitution Tyr486Asp (page 541, Table 2)(limitations of Claims 3-4, 17). Huang teaches analyzing the serum bilirubin levels for the variants. Huang further teaches analysis of the promoter region of UGT1, and position 686 (Table 2)(limitations of Claim 2, 5-6).

**Response to Arguments**

The response traverses the rejection. The response asserts the claims are drawn to an assay method for drug glucuronidation of UGT and the amendments to the claims overcome the rejection. This argument has been reviewed but is not persuasive. The wherein clause that has been added appears to be an inherent property of the

detection of the polymorphism. The clause does not provided any further requirements. The method of Huang which detects the claimed mutation would inherently meet the requirements of the wherein clause. The wherein clause states that the detection of the mutation determines the enzymatic activity. Thus, Huang detects the mutation and must similarly determine the enzymatic activity. Thus for the reasons above and those already of record, the rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 10, 13, 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang et al. (Pharmacogenetics, Vol. 10, pages 539-544, 2000) in view of Heinrich et al. (US Publication 2005/0032724 A1, February 10, 2005).

Huang et al teaches variations of the bilirubin uridine-diphosphoglucuronosyl transferase 1A1 gene in healthy Taiwanese individuals. Huang teaches activity of UGT1 may influence the concentration of serum bilirubin. Huang teaches a variation site in UGT1A1 gene in exon 5, at nucleotides 1456 which is a TAC to GAC substitution which corresponds to the amino acid substitution Tyr486Asp (page 541, Table 2)(limitations of Claims 3-4, 17). Huang teaches analyzing the serum bilirubin levels for

the variants. Huang further teaches analysis of the promoter region of UGT1, and position 686 (Table 2)(limitations of Claim 2, 5-6).

Huang does not specifically teach a method which uses SEQ ID NO: 1 and SEQ ID NO: 2 and/or 3.

However, Heinrich et al. teaches probes and primers for analyzing the UGT1A1 T>G 1471 polymorphism and the UGT1A1 G>A 226 polymorphism. Heinrich teaches a probe sequence of SEQ ID NO: 97-100 which comprises instant SEQ ID NO: 1.

```
Qy          1 TGGTACCAGNACCATTCCT 19
              ||||||||| |||||||||
Db          2 TGGTACCAGGACCATTCCT 20
```

Moreover Heinrich teaches a probe sequence of SEQ ID NO: 9-12 which comprises instant SEQ ID NO: 2.

```
Qy          1 TCAGAGACNGAGCATTTT 18
              |||||||| |||||||||
Db         19 TCAGAGACRGAGCATTTT 2
```

Therefore, it would have been prima facie obvious at the time the invention was made to have used the allele specific primers/probes of Heinrich for the detection of the UGT1A1 polymorphisms taught by Huang. The ordinary artisan would have been motivated to have used known probes so that additional probes would not have to be authenticated prior to use.

**Response to Arguments**

The response traverses the rejection. The response asserts that Huang does not teach a method for drug glucuronidation and the claims are drawn to an assay method for drug glucuronidation of UGT. This argument has been reviewed but is not

persuasive. The wherein clause that has been added appears to be an inherent property of the detection of the polymorphism. The clause does not provided any further requirements. The method of Huang which detects the claimed mutation would inherently meet the requirements of the wherein clause. The wherein clause states that the detection of the mutation determines the enzymatic activity. Thus, Huang detects the mutation and must similarly determine the enzymatic activity. Thus for the reasons above and those already of record, the rejection is maintained.

***Conclusion***

**10. No claims allowable.**

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg

**Jeanine Goldberg**
**Primary Examiner**
January 9, 2008